Basel Epidemiology Seminar

Pregnancy Research

Conny Berlin

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Novartis

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NOVARTIS | Reimagining Medicine

Pregnancy and Medication Use*

Six million pregnancies in US every year

By 2008, approximately ??? of pregnant women reported taking at least one medication

*Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

Pregnancy and Medication Use*

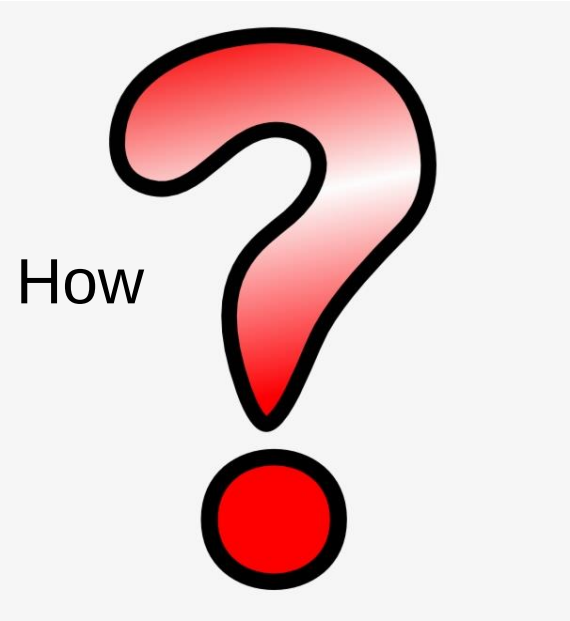
Six million pregnancies in US every year

By 2008, approximately 50% of pregnant women reported taking at least one medication

Pregnant women take an average of 2.6 medications at any time during pregnancy

*Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

Drug labels should provide information which enables decisions for treatment during pregnancy.



FDA – PLLR* Guidance for Industry

A. 8.1 Pregnancy

1. *Pregnancy Exposure Registry*
2. *Risk Summary*
   a. Risk statement based on human data
   b. Risk statement based on animal data
   c. Risk statement based on pharmacology
3. *Clinical Considerations*
   a. Disease-Associated Maternal and/or Embryo/Fetal Risk
   b. Dose Adjustments During Pregnancy and the Postpartum Period
   c. Maternal Adverse Reactions
   d. Fetal/Neonatal Adverse Reactions
   e. Labor or Delivery
4. *Data*
   a. Human Data
   b. Animal Data

*PLLR = Pregnancy and Lactation Labeling Rule

Pregnancy Exposure Registry

- Pregnancy Exposure Registry

  “There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (*name of drug*) during pregnancy.”

- Includes specific contact information

  Phone # & Website

Risk statement based on human data

- Human data can come from
  - Clinical trials
  - Pregnancy exposure registries
  - Other large-scale epidemiologic studies
  - (Well-documented case series)

- Adverse event developmental outcomes – required information
  - Incidence
  - Effect of dose
  - Effect of duration of exposure
  - Effect of gestational timing of exposure

  compared to other drugs in the same indication / condition; general population

Are COVID-19 vaccines safe in pregnancy ?

PFIZER-BIONTECH COVID-19 VACCINE

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of Pfizer-BioNTech COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

labeling.pfizer.com/ShowLabeling.aspx?id=14471, 25 Feb 2021

MODERNA COVID-19 VACCINE

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Moderna COVID-19 Vaccine during pregnancy. Women who are vaccinated with Moderna COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by calling 1-866- MODERNA (1-866-663-3762).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of Moderna COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, fetal development or postnatal development were reported in the study.

DailyMed - MODERNA COVID-19 VACCINE- cx-024414 injection, suspension (nih.gov), 11 Jan 2021

Astra Zeneca COVID-19 VACCINE

Pregnancy

There is limited experience with use of COVID-19 Vaccine AstraZeneca in pregnant women.

Animal reproductive toxicity studies have not been completed. Based upon results from the preliminary study, no effects are expected on development of the fetus (see section 5.3).

Administration of COVID-19 Vaccine AstraZeneca during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether COVID-19 Vaccine AstraZeneca is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

COVID-19 Vaccine AstraZeneca, COVID 19 Vaccine (ChAdOx1 S [recombinant]) (europa.eu), 29 Jan 2021

Are COVID-19 vaccines safe in pregnancy?* UK data

Table 1 | **Accidental pregnancies in trials for the COVID-19 vaccines approved in the United Kingdom**

Vaccine type	Control group			Vaccinated group			Ref.
	Participants	Pregnancies	Miscarriages (rate)	Participants	Pregnancies	Miscarriages (rate)	
Pfizer/BioNTech	18,846	12	1 (8%)	18,860	11	0 (0%)	4
Moderna	15,170	7	1 (14%)	15,181	6	0 (0%)	5
AstraZeneca	5,829	9	3 (33%)	5,807	12	2 (17%)	6

*Male V. Are COVID-19 vaccines safe in pregnancy? Nature Reviews Immunol 2021:1–2
Published on 3 Mar 2021

Are COVID-19 vaccines safe in pregnancy?* US data

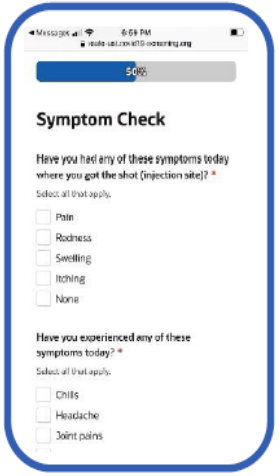
COVID-19 vaccine safety update

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team

* CDC Presentation

Use your smartphone to tell CDC about any side effects after getting the COVID-19 vaccine. You'll also get reminders if you need a second vaccine dose.



1. text message check-ins from CDC (daily 1st week; weekly thru 6 weeks; then 3, 6, and 12 mo.)

vaccine recipient completes web survey*

Vaccine recipients

v-safe℠ after vaccination health checker

2. clinically important health impact reported

✓ **received medical care**

Call center

3. **V-safe** call center conducts active telephone follow-up on a clinically important event and takes a VAERS report if appropriate

4. pregnancy registry team conducts outreach to assess eligibility for registry and obtain consent for enrollment and follow-up

Call center

* Selected web surveys capture information on pregnancy status

Summary of v-safe data as of February 16, 2021

	Pfizer-BioNTech	Moderna	Total
People receiving 1 or more doses in the United States*	28,374,410	26,738,383	55,220,364
Registrants completing at least 1 v-safe health check-in	1,776,960	2,121,022	3,897,982
Pregnancies reported to v-safe†	16,039	14,455	30,494

* COVID Data Tracker as of Feb 16, 2021 (107,571 doses with manufacturer not identified)
† Self-reported during a **v-safe** health check-in

V-safe pregnancy registry

- **V-safe** participants who report pregnancy following COVID-19 vaccination are actively contacted to enroll in pregnancy registry*
- Participants are contacted once per trimester, after delivery, and when the infant is 3 months old†
- Outcomes of interest include miscarriage and still birth, pregnancy complications, maternal intensive care unit admission, adverse birth outcomes, neonatal death, infant hospitalizations, and birth defects

* Must be registered in **v-safe** and have been pregnant at the time of COVID-19 vaccine receipt or within 30 days of vaccination; enrollment may discontinue when sufficient enrollment numbers are achieved

† Phone surveys are conducted along with maternal and infant medical record review

V-safe pregnancy registry enrollment as of February 19, 2021

Registry participants to date (N = 1,949)	
Enrolled	1,815
Not eligible*	103
Refused/declined†	31

- In the enrolled population, there have been 275 completed pregnancies, including 232 live births
  - Other outcomes include miscarriage, stillbirth, ectopic/tubal, other

* Eligibility assessment determines whether vaccination was during pregnancy or within 30 days of last menstrual period

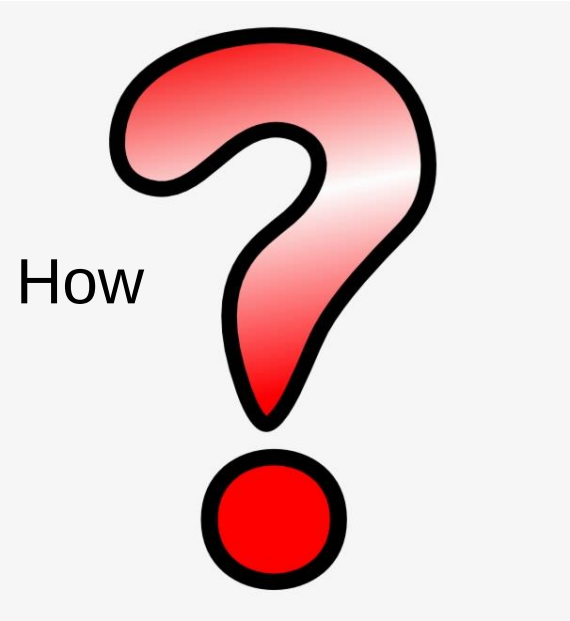
† Refused indicates those for whom eligibility could not be fully assessed because participant chose not to engage with pregnancy registry team; declined indicates those who were eligible to participate but chose not to enroll

V-safe pregnancy registry outcomes of interest in COVID-19 vaccinated pregnant women as of February 18, 2021*

Outcomes	Background rates*	V-safe pregnancy registry overall
Pregnancy outcome		
Miscarriage (<20 weeks)	26%	15%†
Stillbirth (≥ 20 weeks)	0.6%	1%
Pregnancy complications		
Gestational diabetes	7-14%	10%
Preeclampsia or gestational hypertension§	10-15%	15%
Eclampsia	0.27%	0%
Intrauterine growth restriction	3-7%	1%
Neonatal		
Preterm birth	10.1%	10%
Congenital anomalies‡	3%	4%
Small for gestational age^	3-7%	4%
Neonatal death	0.38%	0%

* Sources listed on slide 33; † 93% of these were pregnancy losses <13 weeks of age; § Pre-eclampsia or gestational hypertension diagnosed during pregnancy and/or during delivery; ‡ Congenital anomalies (overall) diagnosed after delivery only; ^ Birthweight below the 10th percentile for gestational age and sex using INTERGROWTH-21st Century growth standards

Drug labels should provide information which enables decisions for treatment during pregnancy.



Today's agenda

14:15 – 14:45	**Julia Spöndlin (University Basel)** Building a mother-baby cohort using Swiss claims data
14:45 – 15:15	**Tania Schink (BIPS, Bremen)** Establishment of a framework to study the utilization and safety of drugs during pregnancy in the German Pharmacoepidemiology Research Database (GePaRD)
15:15 – 15:30	**Break**
15:30 – 16:00	**Lisa Prach (Novartis, Basel)** Evolving strategies to address health authority requests in reproductive toxicity: an industry perspective
16:00 – 16:30	**Kiliana Suzart-Woischnik (Bayer, Berlin)** Experience from the Betaferon pregnancy registry
16:30 – 17:00	**Panel discussion**